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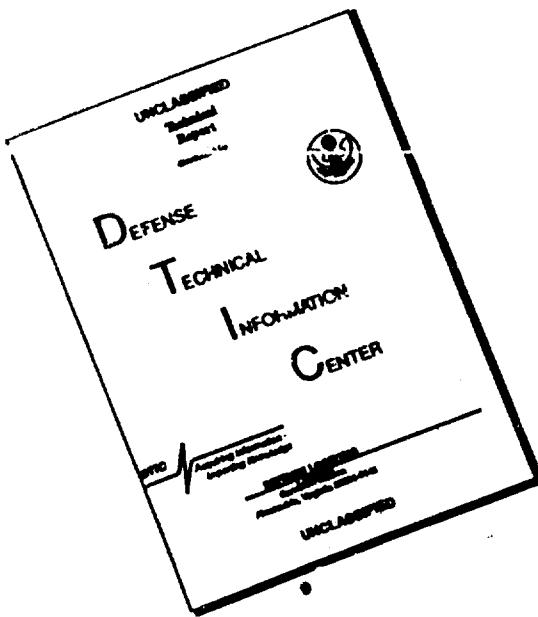
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On the Mechanism of Respiratory Paralysis in Botulism, Tetanus
and Diphtheria

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Described in clinical and experimental reports (1 to 4, 6, 7,
10 and 12) are considerable changes in the function of the respiratory
apparatus caused by botulism, tetanus and diphtheria. It is
assumed that in such neurotoxic cases the cause of death is a pa-
ralysis of the respiratory center. Yet, it is still not clear, whether
neurotoxins render their paralyzing effect on cells of the respira-
tory centers. Still less explored are the mechanisms and their ef-
fects on conduction paths and on motor neurons of the respiratory
muscles.

A task of the current research was to investigate pathological
effects of botuline, tetanus and diphtheria toxins on individual
nerve groups of the respiratory apparatus, also on respiratory
centers with descending conduction paths and on spinal motor centers
of respiratory muscles.

Experiments were carried out on cats and dogs poisoned with botuline toxins type A (1 Dlm for a mouse = 0.00001 mg of dry toxin), with tetanus (1 Dlm = 0.000081 mg) and diphtheria (1 Dlm for a guinea pig = 0.003 ml). The "generalization" of the neuro-intoxication in cats was accomplished with the aid of intravenous administration of poisons in the following doses: botuline toxin 0.5 to 1.5 mg/kg, tetanus 2 to 3 mg/kg and diphtheria 0.1 ml/kg. "Local" involvements of a single diaphragm cupula were effected by way of intramuscular injections of toxins in the following doses: botuline toxins 0.05 to 0.1 mg/kg, tetanus 0.1 to 0.5 mg/kg and diphtheria 0.001 ml/kg. "Local" forms of infections in dogs were developed by administration of poisons into a nerve trunk in the following doses: botuline toxin 0.05 to 0.1 mg/kg and tetanus 0.05 to 0.08 mg/kg.

Sensitive experiments were performed on poisoned and not poisoned animals that were under urethane narcosis (1 gm/kg). The respiratory movements were recorded with the aid of MAREY'S capsule connected with a pressure cuff, or with a tracheal tube. Contractions of the diaphragm cupulae were recorded separately by two isotonic myographs. Respiratory reflexes were induced with the stimulation of the central end of the vagus nerve in the neck as a result of direct current impulses produced by a generator (length of impulses 0.65 m/sec; frequency 1 to 500 imp/sec). The cross diaphragmatic phenomenon was rendered according to the method described in several reports (11 to 16).

In all, we used in experiments 116 cats and 50 dogs, of which 15 cats and 21 dogs were control animals.

Experimental Results

In the presence of the spinal cord's hemisection above the diaphragmatic nerve nucleus, the contractions of paralyzed diaphragm cupulae could be restored by way of blocking or cutting the diaphragmatic nerve on the opposite side. A similar restoration could be effected by inclusion of cross links between the intact inspiratory reticulo-spinal fibers and the motor nucleus of the diaphragmatic nerve at the site of hemisection (11 to 16). This effect, known as a cross diaphragmatic phenomenon, was used in analysis of the mechanisms of bacterial neurotoxic effects on individual links of the neural respiratory apparatus. In the first series of experiments we investigated the functional condition of the respiratory center and of the conduction paths at a site of the local involvement of the diaphragm by botuline, tetanus and diphtheria toxins. Thus, having produced the cross diaphragmatic phenomenon by way of the spinal cord's hemisection at a "healthy" site, we performed ~~of~~ a neurotomy of the diaphragmatic nerve at the involved site.

In 13 experiments on cats and dogs, performed on the 5th to 21st day following their inoculation with botuline toxin, we determined that 1. the function of the respiratory center and of the conduction paths did not undergo any changes at the paralyzed diaphragmatic cupula's site and 2. the cross diaphragmatic phenomenon was noted in all experiments.

The results of other 49 experiments on cats and dogs with a local involvement of tetanus in the diaphragm proved that the cross diaphragmatic phenomenon appeared promptly on the 6th or 7th day

after inoculation and, as a rule, it faded away much later (in the 2d or 3d week). Data similar to those above were also obtained from 29 experiments on cats with a local involvement of diphtheria in the diaphragm; the cross phenomenon^B was also noted within the first 12 days following the inoculation and it vanished by the 20th or 22d day.

Thus, the results of experiments with the instances of various local nerve intoxications showed that familiar distinctions existed in the involvement mechanism of the diaphragmatic innervation apparatus, namely, the pathological process during botulism was (regardless of the stage of intoxication) apparently confined to the motor neurons of the diaphragmatic nerve, whereas a comparatively quick disappearance of the cross phenomenon during tetanus and diphtheria indicated that more complicated involvements existed here and they probably included more than one link of the neural apparatus of respiration.

In the second series of experiments we strived to clarify whether cross connections collaborate between the inspiratory reticulo-spinal paths and the motor nuclei of the diaphragmatic nerve in compensatory processes during respiratory insufficiencies after grave and generalized forms of botulism, tetanus and diphtheria had developed.

We recorded a preservation of the cross diaphragmatic phenomenon in all instances during 8 experiments on cats inoculated with tetanus and in 5 experiments with diphtheria, even after a very grave intoxication had developed. The phenomenon coincided in its essence with that observed in control animals. In analogous

experiments with botulism, where a usual reproduction technique was applied, the cross diaphragmatic phenomenon was observed only

Figure 1 - Absence of diaphragm paralysis at the site of the spinal cord hemisection in a cat inoculated with botuline toxin. Paralytic syndrome is not evident. Contractions of diaphragmatic cupulae were recorded up to (A) and after (B) a section of the spinal cord. Arrow indicates a section of the right diaphragmatic nerve. Below is the indication of time (5 seconds).

in the presence of mild indicants of involvement (light paresis of skeletal muscles). In the presence of expressed paralytic botuline syndrome, the hemisection of the spinal cord was not accompanied by a usual one-sided paralysis of the diaphragm (figure 1). The appearance of the cross diaphragmatic phenomenon in the absence of the diaphragmatic nerve section (on the opposite page) undoubtedly indicated a considerable activation of the cross links and their inclusion in the mechanisms that compensate for respiratory insufficiencies, the aftermath of severe botulism.

The accuracy of such inclusion has been confirmed in experiments with a section of the diaphragmatic nerve at a site opposite

Figure 2 - Absence of diaphragm paralysis at a site of prior hemisection of the spinal cord in a cat infected with botuline toxin. A general paralytic syndrome. A - paralysis of a diaphragm cupula at the intact site; B - contractions of diaphragm cupula at the site of prior hemisection of the spinal cord. Below is the indication of time (5 seconds).

the hemisection of the spinal cord. Under these conditions, in 7 out of 17 experiments described above, the exhaustion of contractile activity in the functioning part of diaphragm began in 30 to 150 seconds after the nerve section, then decompensation in the respiration developed and the animal had to die unavoidably, unless they were administered artificial respiration. A disengagement of artificial respiration for some time caused a repeated temporary restoration of the diaphragm contractions at a site of the hemisection of the spinal cord. Obtained data suggested that, in the

case of botulism, the diaphragm paralysis occurred not as a result of exclusion of the respiratory center activity and that of the conduction paths, but due to a sharp decrease in the excitability and in the efficiency of the motor neurons' nuclei in the diaphragmatic nerve.

The last assumption served as a basis for conducting the third series of experiments. Their purpose was to investigate the function of the neural respiratory apparatus with the background of non-concurrent inoculation of diaphragmatic nerve nuclei using the toxins of botulism, tetanus and diphtheria. We proceeded from a standpoint that, after an inhibition of nerve centers, their involvement by bacterial neurotoxins can seldom be retarded (5, 9). A prolonged inhibition of a single nucleus of diaphragmatic nerve was produced by hemisection of the spinal cord at the level of the II cervical vertebra. Thus, the function of diaphragm was not disturbed in cats at the intact site, whereas the function at the paralyzed site could be restored exclusively at the expense of the activation of cross links. The animals so prepared were inoculated (as in previous experiments) with fatal doses of botuline, tetanus and diphtheria toxins. In all, 22 experiments were performed on operated animals having a generalized botulism, 15 experiments with tetanus and 11 experiments with diphtheria.

The results of experiments proved that during a grave stage of tetanus and diphtheria intoxications cats died within the same time periods as control animals and manifested no restorations of the diaphragm contractions at the site of prior hemisection of the spinal cord. Yet, the fact that in similar experiments a section of

the diaphragmatic nerve at the opposite site caused the appearance of the cross diaphragmatic phenomenon, this indicated a preservation of the cross links during these intoxications. In cats with a prior section of the spinal cord, the involvement picture of botuline toxin differed noticeably from that observed in control animals. The operated animals, having received a fatal dose of toxin, lived until the 3rd to 5th day, while the control animals died on the 2d day.

General clinical observations and mechanographic recordings of the diaphragm contractions revealed that, in the early stages of intoxication in cats infected with botulism, the cross diaphragmatic phenomenon was reproduced only according to the "classificatory" technique and following the neurotomy of the opposite diaphragmatic nerve. We observed in aforescribed stages of the paresis expressed in skeletal muscles and in experiments the presence of contractions in both cupulae of the diaphragm. Yet, with the development of general paralyses (figure 2), the diaphragmatic contractions dropped completely at the intact site, while at the site of the hemisection of the spinal cord the diaphragm contractions continued for a long time (up to 2 days). Owing to the compensatory mechanism of respiration, the operated animals continued to live longer after the operation than the control animals. Thus, the experimental results obtained from generalized botulism indicated that a temporary delay in inoculation of a single nucleus of the diaphragmatic nerve, caused by a prior hemisection of the spinal cord, permits this nucleus to function for a long ~~time~~ even with the background of a complete exclusion of activity

in other sections of the motor innervation in skeletal muscles. This indicates that the cause of death in generalized botulism is not a paralysis of the respiratory centers, nor that of the conduction paths, but a sharp depression in the activity of the motor innervation in respiratory muscles.

As the analysis of respiratory disorders indicates in local and generalized forms of bacterial neurotoxications, the mechanisms of the paralytic action of botulism toxin on respiratory muscles is obviously the same as in other sections of skeletal muscles (8). It is essential to distinguish the development rules of respiratory disorders in diphtheria and in tetanus from those described under botulism, including, of course, a whole series of links of the innervation apparatus. A clarification of these questions requires additional investigations.

Literature Cited

1. ABROSIMOV, V.N. Arkh. Pat. 1956, p.86.- 2. The same. Book: Problems in pathological physiology of infection processes. Moscow, 1962, p.17.- 3. The same. Path. Physiol. 1962, No.3, p.44.- 4. GARANINA, I.P. Byull. Eksp. Biol., 1958, No.11, p.42. - 5. GOLDFARB, D.M. and PEISAKHIS, L.A. Zh. Mikrob. 1953, No.9, p.63. - 6. KORITSKII, A.M. Book: Botulism. Dnepropetrovsk, 1937, p.91. - 7. KRIZHANOVSKII, G.N. Book: Physiology and pathology of blood circulation and respiration. Moscow, 1960, p.113. - 8. MIKHAILOV, V.V. Pathophysiological mechanisms in experimental botulism. Dissertation. Moscow, 1959. 9. PLETSITYI, D.P. Book: Reaction problems in pathology. Moscow, 1954, p.34. - 10. FEDOROV, B.M. and PODREZOVA, N.A. Book: Physiology and pathology of blood circulation and respiration.

Moscow, 1960, p.29. - 11. CHATFIELD, P.O. and MEAD, S. Amer. Journ. Physiol., 1948, vol.154, p.417. - 12. DAVIES, J.R., MORGAN, R.S., WRIGHT, E.A. et al. Journ. Physiol. (London), 1953, vol.120, p.618. - 13. LEWIS, L.J. and BROOKHART, J.M. Amer. Journ. Physiol., 1951, vol. 166, p.241. - 14. PORTER, W.T. Journ. Physiol. (London), 1894/1895, vol.17, p. 455. - 15. ROSENBLUETH, A. and ORTIZ, T. Amer. Journ. Physiol., 1936, vol.117, p.495. - 16. ROSENBLUETH, A., KLOPP, C.T. and SIMONE, P.A. Journ. Neurophysiol., 1938, vol. 1, p.508.

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Using the cross diaphragmatic phenomenon as an illustration, the authors demonstrated that respiratory paralysis in botulism was caused by depression of motor innervation function of respiratory muscles and not by the exclusion of the respiratory center activity.

Disturbances of respiration in tetanus and diphtheria are due to another, more complicated mechanism.